EFFECTS OF THYROXINE REPLACEMENT ON GLYCOSYLATED HEMOGLOBIN LEVELS IN NON DIABETIC PATIENTS WITH OVERT HYPOTHYROIDISM.

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CHENNAI, TAMILNADU

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled “EFFECTS OF THYROXINE REPLACEMENT ON GLYCOSYLATED HEMOGLOBIN LEVELS IN NON DIABETIC PATIENTS WITH OVERT HYPOTHYROIDISM. ” is the bonafide work of Dr. DEEPIKA SAKTHISEKARAN in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in May 2019.

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DECLARATION

I, Dr.DEEPIKA SAKTHISEKARAN solemnly declare that, this dissertation "EFFECTS OF THYROXINE REPLACEMENT ON GLYCOSYLATED HEMOGLOBIN LEVELS IN NON DIABETIC PATIENTS WITH OVERT HYPOTHYROIDISM. is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of Dr.R.BALAJINATHAN,M.D., Professor, Department of General Medicine, Madurai Medical college, Madurai. This dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D Degree General Medicine Branch-I examination to be held in May 2019.

Place: Madurai

Date: Dr. DEEPIKA SAKTHISEKARAN

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INTRODUCTION

HbA1c is used for screening as well as for diagnosing Diabetes Mellitus.

HbA1c - 4% – 5.7% - normal

5.7%- 6.5% - pre-diabetes

> 6.5% - diabetes mellitus.

It depends on ambient levels of glycemia over the preceeding 2-3 months but also on the RBC turnover from the bone marrow. HbA1c may not accurately reflect the level of glycemia in conditions of altered erythrocyte turnover.

Conditions which are associated with a low RBC turnover (hypoproliferative anemias) are associated with a falsely elevated HbA1c.

Hypothyroidism being one of the causes of hypoproliferative anemia may lead to false elevation of HbA1c resulting in erroneous diagnosis of pre diabetes or diabetes.

AIMS AND OBJECTIVES

- The objective of our study was to determine the effects of hypothyroidism on HbA1c levels in individuals without diabetes.

- To observe whether HbA1c falls in hypothyroid patients following treatment.

- To assess the validity of using HbA1c for diagnosing diabetes in hypothyroid patients.

REVIEW OF LITERATURE

ANATOMY OF THYROID

The thyroid gland is located anteriorly in the neck, extending from the fifth cervical vertebra to the first thoracic vertebra The gland consists of 2 elongated lateral lobes with superior and inferior poles connected by a median isthmus, with an height of 12-15 mm, overlying the second to fourth tracheal rings. Thyroid weight varies between 25-30 g in adults . The gland enlarges during menstruation and pregnancy.

Innervation of the thyroid gland is from the autonomic nervous system. Parasympathetic fibers come from the vagus nerves, and sympathetic fibers are distributed from the superior, middle, and inferior ganglia of the sympathetic trunk.

HISTOLOGY OF THYROID

The thyroid has an inner capsule which divide it into lobes and lobules. The lobules are composed of follicles, which are the structural units of the gland, which consist of a layer of simple epithelium enclosing a colloid-filled cavity This colloid contains an iodinated glycoprotein, iodothyroglobulin, a precursor of thyroid hormones.

Epithelial cells are of 2 types: principal cells (ie, follicular) and parafollicular cells (ie, C, clear, light cells). Principal cells are responsible for formation of the colloid - iodothyroglobulin, whereas parafollicular cells produce the hormone calcitonin, a protein central to calcium homeostasis. Parafollicular cells lie adjacent to the follicles within the basal lamina.

BLOOD SUPPLY

The arterial supply to the thyroid gland comes from the superior and inferior thyroid arteries and, occasionally, from the thyroidea ima. These arteries have abundant collateral anastomoses with each other The thyroid ima is a single vessel that, when present, originates from the aortic arch or the innominate artery and

enters the thyroid gland at the inferior border of the isthmus.Three pairs of veins provide venous drainage for the thyroid gland.

The superior thyroid vein passes along the superior thyroid artery and becomes a tributary of the internal jugular vein. The middle thyroid vein follows a direct course laterally to the internal jugular vein. The inferior thyroid veins follow different paths on each side. The right passes anterior to the innominate artery to the right brachiocephalic vein or anterior to the trachea to the left brachiocephalic vein.On the left side, drainage is to the left brachiocephalic vein.

Immediate lymphatic drainage courses to the periglandular nodes; to the prelaryngeal (Delphian), pretracheal, and paratracheal nodes along the recurrent laryngeal nerve; and then to mediastinal lymph nodes.

DEVELOPMENT OF THYROID

The thyroid gland appears in the floor of the pharynx at the base of the tongue between the tuberculum impar and the copula linguae at 3–4 weeks gestational age.

The thyroid then descends in front of the pharyngeal gut as a bilobed diverticulum through the thyroglossal duct. Over the next few weeks, it migrates to the base of the neck, passing in front of the hyoid bone. During migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct. At the end of the fifth week the thyroglossal duct degenerates and the detached thyroid continues on to its final position over the following two weeks.

The fetal hypothalamus and pituitary start to secrete thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH). TSH starts to secretes by 11 weeks. By 18–20 weeks, the production of thyroxine (T4) reaches a self-sufficient level. Fetal triiodothyronine (T3) remains low, less than 15 ng/dL until 30 weeks, and increases to 50 ng/dL at full-term.

The fetus needs to be self-sufficient in thyroid hormones in order to guard against neurodevelopmental disorders that would arise from maternal hypothyroidism. The presence of sufficient iodine is essential for healthy neurodevelopment.

The neuroendocrine parafollicular cells, also known as C cells, responsible for the production of calcitonin, are derived from foregut endoderm. This part of the thyroid then first forms as the ultimopharyngeal body, which begins in the ventral fourth pharyngeal pouch and joins the primordial thyroid gland during its descent to its final location.

Aberrations in prenatal development can result in various forms of thyroid dysgenesis which can cause congenital hypothyroidism, and if untreated this can lead to cretinism.

PHYSIOLOGY OF THYROID GLAND

There are six steps in the synthesis of thyroid hormone

Active transport of Iodide into the follicular cell via Sodium-Iodide Symporter (NIS).

This is actually secondary active transport, and the sodium gradient driving it is maintained by a Sodium-Potassium ATPase.

- **Thyroglobulin** (Tg), a large protein rich in Tyrosine, is formed in follicular ribosomes and placed into secretory vesicles.

- **Exocytosis** of Thyroglobulin into follicle lumen, where it is stored as colloid. Thyroglobulin is the scaffold upon which thyroid hormone is synthesised.

- **Iodination** of the Thyroglobulin. Iodide is made reactive by the enzyme thyroid peroxidase. Iodide binds to the benzene ring on Tyrosine residues of Thyroglobulin. First formed is monoiodotyrosine (MIT) then diiodotyrosine (DIT).

- **Coupling** of MIT and DIT to give Triiodothyronine (T3) hormone and coupling of DIT and

DIT to give Tetraiodothyronine (T4) hormone, also known as Thyroxine.

- **Endocytosis** of iodinated thyroglobulin back into the follicular cell.

Thyroglobulin undergoes proteolysis in lysosomes to cleave the iodinated tyrosine residues from the larger protein. Free T3 or T4 is then released, and the Thyroglobulin scaffold is recycled.

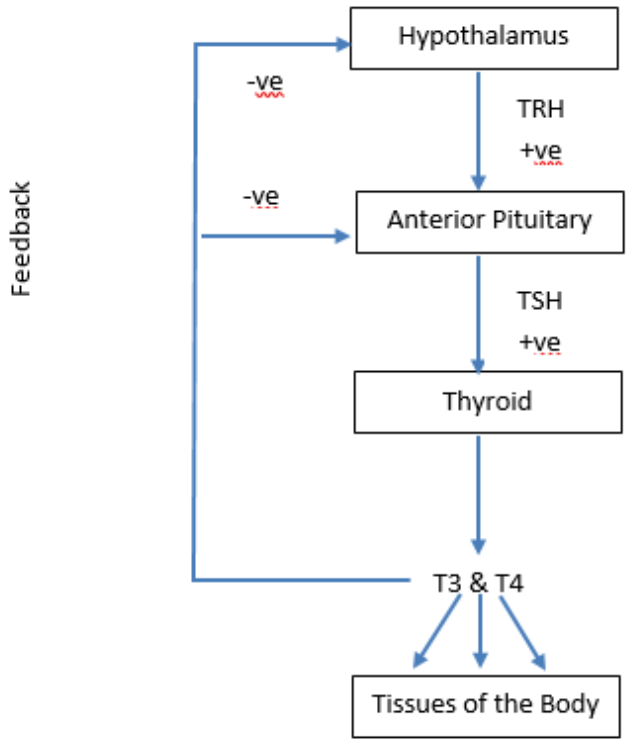
T3 and T4 are the active thyroid hormones. They are **fat soluble** and mostly carried by plasma proteins – Thyronine Binding Globulin and Albumin. While T3 is the more potent, it also has a shorter half-life (T3 half life – 1-2 days. T4 half life – 6-7 days)due to its lower affinity for the binding proteins. Less than **1%** of T3 and T4 is unbound free hormone. At the peripheries, T4 is deiodinated to the more active T3.

T3 and T4 are deactivated by removing iodine. This happens in the liver and kidney. As T4 has a longer half-life it is used in the treatment of hypothyroidism over T3 as its plasma concentrations are easier to manage.

HYPOTHALAMO PITUITARY AXIS

The hypothalamus produces Thyrotrophin Releasing Hormone **(TRH).** TRH stimulates thryotroph cells in the anterior pituitary to produce Thyroid Stimulating Hormone (TSH).

TSH is released in low amplitude pulses, following a circadian rhythm (In this case, there are higher levels at night and lower levels in the morning). TSH binds to receptors on follicular cells of the thyroid gland, stimulating the production of thyroid hormones: Tri-iodothyronine **(T3)** and Tetra-iodothyronine **(T4),** also known as Thyroxine. Control of this system is by a negative feedback mechanism: high levels of T3 and T4 inhibit TRH and TSH production by the hypothalamus and anterior pituitary gland, respectively.



FUNCTIONS OF THYROID HORMONES

Increase Basal Metabolic Rate (BMR),

Increase Oxygen consumption,

• Increase Thermogenesis (heat production in the body),

• Activate Na+ -K + -ATPase in cells,

• Increase number of Mitochondria in cells

• Increase mobilization of endogenous: Carbohydrate, Fat and Protein as substrates for energy metabolism,

• Increase Glycolysis, Glycogenolysis, Gluconeogenesis,

• Increase Lipolysis and Protein degradation,

• Decrease Muscle mass,

• Decrease Adipose Tissue,

• Increase Beta-Adrenergic receptors, which leads to increase Cardiac Output,

• Increase Systolic blood pressure only,

• Increase Ventilation Rate,

• Required for maturation of Ovary and Testis,

• Required for Actions of Growth Hormone (GH) to promote linear growth / bone formation,

• Required for development of CNS in Foetus.

LABORATORY MEASUREMENT OF THYROID HORMONES

Serum-based methods are available for measuring both total (TT4 and TT3) and free (FT4 and FT3) thyroid hormone concentrations.

• In addition, measurements can be made of the thyroid hormone binding proteins, Thyroxine Binding globulin (TBG), Transthyretin (TTR)/Prealbumin (TBPA) and Albumin, as well as for the pituitary thyroid stimulator, thyrotropin (thyroid stimulating hormone, TSH) and the thyroid hormone precursor protein, Thyroglobulin (Tg).

• The recognition of autoimmunity as the leading cause of thyroid dysfunction, has led to the development and incorporation of tests to determine thyroid autoantibodies – thyroid peroxidise antibodies (TPOAb), thyroglobulin antibodies (TgAb), and TSH receptor antibodies (TRAb).

1 : Reference values of thyroid function test

Test Range

TSH - 0.5 -4.7mU/L

T3 - 0.92-2.78nmol/L

FT3 -0.22-6.78 pmol/L

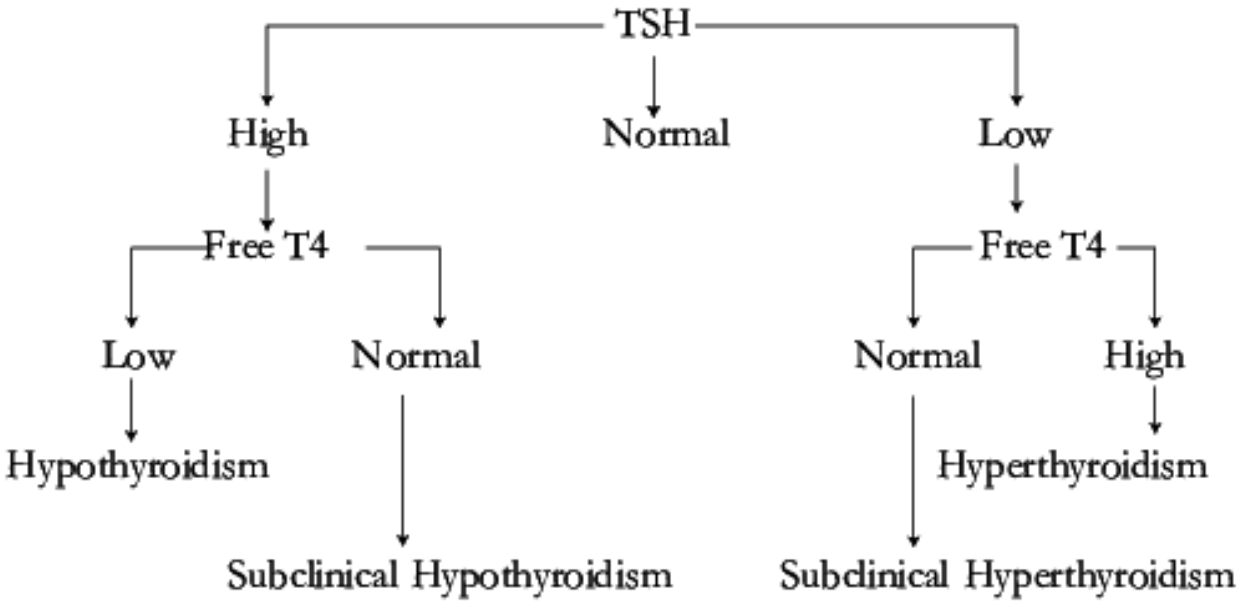
T4 -58-140 nmol/L

FT4 -10.3-35pmol/L

The sensitive immunoradiometric assays (IRMA) for TSH are sensitive enough to distinguish between the lower limit of the reference range or suppressed values of TSH that are seen in thyrotoxicosis. Extremely sensitive TSH assays are now available; the 4th/5th generation assays can detect TSH levels as low as 0≤0.004mU/L. However, for practical purposes, TSH values of ≤ 0.1mU/L are considered sufficient. If TSH levels are found to be abnormal, then circulating T3 and T4 levels should be estimated. Although radioimmuno assays are widely available to measure total T3 and T4, these are highly protein bound and several factors can influence their levels. Hence it is important to measure free or unbound T3 and T4 levels.

Currently routine measurement of serum T3 is not carried out (only T4 is measured) in patients suspected of having thyroid disorders. About 25% of patients with hypothyroidism have low normal T3 values. Free T3/ total T3 measurements, however, should be performed in the following settings: 1. In patients suspected of having T3 thyrotoxicosis. 2. In patients taking drugs that inhibit the peripheral conversion of T4 to T3 (such as dexamethasone, propranolol, propylthiouracil, amiodarone, and iodine-containing contrast media).

Tests for antibodies against thyroid-specific antigens, antithyroid peroxidase (TPO), thyroglobulin (Tg) and TSH receptors are used in the diagnosis of autoimmune thyroid disorders.



THYROID FUNCTION TESTS IN PREGNANCY

The high circulating hCG levels in the first trimester may result in a slightly low TSH (called subclinical hyperthyroidism). When this occurs, the TSH will be slightly decreased in the first trimester and then return to normal throughout the duration of pregnancy. Estrogen increases the amount of thyroid hormone binding proteins in the serum which increases the total thyroid hormone levels in the blood since >99% of the thyroid hormones in the blood are bound to these proteins.

However, measurements of "Free" hormone (that not bound to protein, representing the active form of the hormone) usually remain normal. The thyroid is functioning normally if the TSH, Free T4 and Free T3 are all normal throughout pregnancy.

Trimester	TSH cut-off (μIU/ml)
First trimester	2.0-2.5
Second trimester	3.0
Third trimester	3.5

DRUGS ALTERING THYROID FUNCTION

Use of certain drugs may result in altered thyroid hormone metabolism and require higher doses of replacement LT4 to achieve a normal TSH.

- Increased hepatic enzymes from certain antiepileptic medications (phenobarbital, carbamazepine or phenytoin) and the antibiotic, rifampicin, may reduce the half-lives of T4 and T3
- Imatinib (a tyrosine kinase inhibitor used to treat certain cancers) is thought to increase the hepatic metabolism of thyroid hormone
- Drugs that increase thyroxine binding globulin (TBG) levels (e.g. estrogens) will reduce the availability of FT4
- Amiodarone impairs the peripheral de-iodination of T4, and therefore, the conversion of T4 to T3
- Glucocorticoids and some beta blockers at high doses can also inhibit T4 toT3 de-iodination, although these changes are not usually clinically relevant

HYPOTHYROIDISM

Causes

Primary hypothyroidism	Iodine deficiency , autoimmune thyroiditis, granulomatous thyroiditis, subacute lymphocytic thyroiditis, postpartum thyroiditis, previous thyroidectomy, radioiodine treatment, previous radiotherapy to the neck Medication: lithium, amiodarone, interferon alpha, tyrosine kinase inhibitors
Central hypothyroidim	Lesions of pituitary ,pituitary adenoma, craniopharyngioma, meningioma, glioma, metastasis, empty sella, surgery or radiation to the pituitary, drugs, injury, pituitary apoplexy, Sheehan syndrome, subarachnoid hemorrhage, autoimmune diseases (lymphocytic hypophysitis, polyglandular disorders), infiltrative diseases and infections like tuberculosis, mycoses, syphilis
Congenital hypothyroidism	Thyroid dysgenesis (75%), thyroid dyshormonogenesis (20%), maternal antibody or genetic mutations Transiently: due to maternal iodine deficiency or excess, anti-TSH receptor antibodies, , neonatal illness Central: pituitary dysfunction (idiopathic, septo-optic dysplasia, deficiency of *PIT1*, isolated TSH deficiency)

CENTRAL HYPOTHYROIDISM

In this the TSH level is normal or low and free T_4 levels are low, this is suggestive of central hypothyroidism. There can also be other features of hypopituitarism.

PRIMARY OVERT HYPOTHYROIDISM

TSH levels are high and T_4 and T_3 levels are low. Overt hypothyroidism is diagnosed in those with a TSH of greater than 10mIU/L.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is characterized by an elevated serum TSH level, but with a normal serum free T4. The presentation of subclinical hypothyroidism is variable and classic signs and symptoms of hypothyroidism may not be observed.

Of people with subclinical hypothyroidism, a proportion will develop overt hypothyroidism each year. patient who have subclinical hypothyroidism are treated if the patient is pregnant or TSH above 10 or if the patient has any underlying heart disease or positive TPO antibodies.

CONGENITAL HYPOTHYROIDISM

Congenital hypothyroidism is a preventable cause of mental retardation. It is caused by thyroid dysgenesis which is a sporadic disorder and accounts for 85% of cases and the remaining 15% of cases are due to dyshormonogenesis.

Dried capillary blood is used for screening and it is taken from heel prick between 2 and 5 days of age. Spot TSH or T4 or both are being used for screening. Levothyroxine is the treatment of choice it is crushed and mixed with breast milki and is spread on to cheek pad or can put on nipple for feeding.

Target values

T4 - 10-16 μgm/dl

FT4 -1.4-2.3ng/dl

TSH- <5 μU/dl for first 3 years of life.

Thereafter, T4 should be kept in the upper half of normal range.

SICK EUTHYROID SYNDROME

Any severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of thyroid disease.

It is due to hormonal changes and release of cytokines IL-6.

The most common hormone pattern in sick euthyroidal is adecrease in total and unbound T3 levels(low T3 syndrome) with normal levels of T4 and TSH.

The magnitude of the fall in T3 correlates with severity of illness.Other spectrum consists of low T4 syndrome. This state has a poor prognosis. TSH levels may range from <0.1 mIU / L especially in patients on dopamine or noradrenaline.

Liver disease and renal disease are associated with low T3 and T4.

TREATMENT OF HYPOTHYROIDISM

Thyroid hormone can be started at anticipated full replacement doses in individuals who are young and otherwise healthy. In elderly patients and those with known ischemic heart disease, treatment should begin with one fourth to one half the expected dosage, and the dosage should be adjusted in small increments after no less than 4-6 weeks. For most cases of mild to moderate hypothyroidism, a starting levothyroxine dosage of 50-75 µg/day will suffice.

Clinical benefits begin in 3-5 days and level off after 4-6 weeks. Achieving a TSH level within the reference range may take several months because of delayed readaptation of the hypothalamic-pituitary axis. In patients receiving treatment with LT4, dosing changes should be made every 6-8 weeks until the patient's TSH is in target range.

In patients with central (ie, pituitary or hypothalamic) hypothyroidism, T4 levels rather than TSH levels are used to guide treatment. In most cases, the free T4 level should be kept in the upper third of the reference range.

The updated guidelines on hypothyroidism issued by the American Thyroid Association in 2014 maintain the recommendation of levothyroxine as the preparation of choice for hypothyroidism, with the following considerations:

If levothyroxine dose requirements are much higher than expected, consider evaluating for gastrointestinal disorders such as Helicobacter pylori –related gastritis, atrophic gastritis, or celiac disease; if such disorders are detected and effectively treated, re-evaluation of thyroid function and levothyroxine dosage is recommended.

Initiation or discontinuation of estrogen and androgens should be followed by reassessment of serum TSH at steady state, since such medications may alter levothyroxine requirement.

Serum TSH should be reassessed upon initiation of agents such as tyrosine kinase inhibitors that affect thyroxine metabolism and thyroxine or triiodothyronine deiodination.

Serum TSH monitoring is advisable when medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline are started.

When deciding on a starting dose of levothyroxine, the patient’s weight, lean body mass, pregnancy status, etiology of hypothyroidism, degree of TSH elevation, age, and general clinical context, including the presence of cardiac disease, should be considered. The serum TSH goal appropriate for the clinical situation should also be considered.

Thyroid hormone therapy should be initiated as an initial full replacement or as partial replacement with gradual increments in the dose titrated upward using serum TSH as the goal.

Dose adjustments should be made upon significant changes in body weight, with aging, and with pregnancy; TSH assessment should be performed 4-6 weeks after any dosage change.

Reference ranges of serum TSH levels are higher in older populations (eg, >65 years), so higher serum TSH targets may be appropriate.

DIABETES AND HYPOTHYROIDISM

Hypothyroidism and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. Diabetes and hypothyroidism mutually influence each other and associations between both conditions have long been reported . On one hand, thyroid hormones contribute to the regulation of carbohydrate metabolism and pancreatic function, and on the other hand, diabetes affects thyroid function tests to variable extents.

In hypothyroidism glucose metabolism is affected via several mechanisms. A reduced rate of liver gluconeogenesis is observed in hypothyroidism and is responsible for lower insulin requirement in hypothyroid diabetic patients. Recurrent hypoglycemic episodes are the presenting signs for the development of hypothyroidism in patients with type 1 diabetes On the other hand, both clinical and subclinical hypothyroidisms have been recognized as insulin resistant states.

Reduced glucose absorption from gastrointestinal tract accompanied by prolonged peripheral glucose accumulation, gluconeogenesis, decreased glycogenolysis and reduced disposal of glucose are hallmarks of hypothyroidism . In overt or subclinical hypothyroidism, insulin resistance leads to glucose-stimulated insulin secretion . In subclinical hypothyroidism, diminished rate of insulin stimulated glucose transport rate caused by perturbed expression of glucose transporter type 2 gene (GLUT 2) translocation may lead to insulin resistance. Moreover, due to reduced renal clearance of insulin in hypothyroid conditions, physiological requirements of insulin were diminished. Anorectic conditions in hypothyroidism may also contribute to reduced insulin in this state. An enhanced dose of insulin is required to ameliorate hypothyroidism, but the therapy warrants caution for adrenal or pituitary failure.Unmanaged diabetes, both type 1 and type 2, may induce a “low T3 state” characterized by low serum total and free T3 levels, increase in reverse T3 (rT3) but near normal serum T4 and TSH concentrations.

Diabetic practice guidelines for thyroid screening in patients with diabetes.

- American Thyroid Association guidelines for detection of thyroid dysfunction –

  Patients with diabetes may require more frequent testing Recommends TSH from 35 yrs, and every 5 yrs thereafter in all adults.

- American Association of Clinical Endocrinologists recommends TSH at diagnosis and at regular intervals, especially if goitre or other autoimmune disease is suspected.

- British Thyroid Association and Association of Clinical Biochemistry Guidelines, 2006 recommends TFT at baseline but routine annual TFT is not recommended.TSH and antibodies are recommended in diabetic patients in pregnancy and postpartum

DIABETES

Diabetes currently affects 425 million adults, a total that is set to reach 629 million by 2045. When not appropriately managed, all types of diabetes can result in complications affecting many parts of the body, leading to frequent hospitalization and early death.

Diabetes is one of the leading causes of cardiovascular disease, with one out of four diabetes inpatient costs a consequence of cardiovascular complications. Diabetic retinopathy is the leading cause of vision loss in working-age adults. The prevalence of end-stage renal disease is up to ten times higher in people with diabetes. Pregnant women with diabetes are at increased risk of maternal and foetal complications.

India, home to the second largest number of diabetes cases (73 million in 2017), With over half of people currently living with diabetes in the country estimated to be undiagnosed, there is urgency to increase awareness and knowledge of diabetes and its associated complications among health professionals to promote screening and early diagnosis to improve health outcomes and help save lives.

ETIOLOGIC CLASSIFICATION OF DIABETES

. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated

B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

A. Genetic defects of β-cell function

1. Chromosome 12, HNF-1α (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4α (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1β (MODY5)
6. Chromosome 2, NeuroD1 (MODY6)
7. Mitochondrial DNA
8. Others

B. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism

3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

C. Diseases of the exocrine pancreas

1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others

D. Endocrinopathies

1. Acromegaly
2. Cushing’s syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others

E. Drug- or chemical-induced

1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. α-Interferon
11. Others

F. Infections

1. Congenital rubella
2. Cytomegalovirus
3. Others

G. Uncommon forms of immune-mediated diabetes

1. “Stiff-man” syndrome
2. Anti-insulin receptor antibodies
3. Others

H. Other genetic syndromes sometimes associated with diabetes

1. Down's syndrome
2. Klinefelter's syndrome
3. Turner's syndrome
4. Wolfram's syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others

IV. Gestational diabetes mellitus (GDM)

COMPLICATIONS OF DIABETES

ACUTE COMPLICATIONS: Hypoglycemia

Diabetic Ketoacidosis

Nonketotic Hyperosmolar Coma.

CHRONIC COMPLICATIONS

Microangiopathic complications:

- Diabetic nephropathy- It is the most common cause of adult kidney failure in the developed world.
- Diabetic neuropathy- commonly a sensori motor polyneuropathy. usually in a 'glove and stocking' distribution. This can also lead to diabetic foot . It may present as mononeuritis or autonomic neuropathy. Diabetic amyotrophy also occurs.
- Diabetic retinopathy.
- Diabetic cardiomyopathy,
- Erectile Dysfunction

MACROVASCULAR COMPLICATIONS

Macrovascular disease occurs due to accelerated atherosclerosis.

- Coronary artery disease

- Peripheral vascular disease

- Cerebro vascular accidents.

- Diabetic foot- due to a combination of sensory neuropathy and vasculopathy.

  Most common cause of non traumatic foot amputation.

- Female infertility – commonly due to PCOD.

DIAGNOSIS OF DIABETES.

1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl. Casual is defined as any time of day without regard to time since last meal. The

classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

Or

2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

Or

3. 2-h postload glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

4. **HbA1C > 6.5%**

5.7-6.5% (Pre diabetes)

WHAT IS HbA1C?

Hemoglobin A1c (HbA1c) is a result of the nonenzymatic attachment of a hexose molecule to the N-terminal amino acid of the hemoglobin molecule. The

attachment of the hexose molecule occurs continually over the entire life span of the erythrocyte and is dependent on blood glucose concentration and the duration of exposure of the erythrocyte to blood glucose. Glycated haemoglobin (HbA1c) reflects average plasma glucose over the previous 8 to 12 weeks.

It can be performed at any time of the day and does not require fasting. These properties have made it the preferredtest for assessing glycaemic control in people with diabetes.

Therapeutic goals for glycemic control (ADA)

-Adults:

- Goal of therapy: <7.0% HbA1c

- Action suggested: >8.0% HbA1c

-Pediatric patients:

- Toddlers and preschoolers: <8.5% (but >7.5%)

- School age (6-12 years): <8%

- Adolescents and young adults (13-19 years): <7.5%

How to measure HbA1c?

A chemical (electrical) charge is present on the molecule of HbA1c, and the amount of the charge differs from the charges on the different components of hemoglobin . The molecule of HbA1c has difference in size from the other components.

HbA1c may be separated by charge and size from the other hemoglobin A components in blood by a procedure known as high pressure (or performance) liquid chromatography (HPLC). HPLC which separates mixtures (for example, blood) into its various components by adding the mixtures to special liquids and passing them under pressure through columns filled with a material that separates the mixture into its different component molecules. Because HbA1c is not affected by short-term fluctuations inblood glucose concentrations, example due to meals, blood can be drawn for HbA1c testing without regard to when food was eaten.

There are 3 major HbA1c testing methods currently available to clinical laboratories.

a. Chromatography based HPLC assay

b. Antibody based immunoassay

c. Enzyme based enzymatic assay

Chromatographic method

HPLC

The chromatographic assay uses an HPLC instrument and ion exchange or affinity column to separate HbA1c molecules from another hemoglobin molecules . The HbA1c content is measured which is based on the ratio of HbA1c peak area to thetotal hemoglobin peak areas.Boronate affinity chromatography: It is based on use of a “biological interaction” for the separation and analysis of specific analytes within a sample. For HbA1c, boronate affinity chromatography is a glycation specific method based on boronatebinding to the unique cis-diol configuration formed by stable glucose attachments to Hb.

This method thus measures all four stable species, altogether. The combined measure of only the four stable species has been referred to as “Total HbA1c “ or by some as “True HbA1c “. Since only two fractions are present in thesemethods (glycated and non-glycated), the glycated portion is compared to the total and results are expressed as % HbA1c. The linearity range for the HbA1c detection is 5.3% to 17%.

Latex enhanced immunoassay method: The latex enhanced immunoassay for HbA1c is based on the interactions between antigen molecules (HbA1c) and HbA1c specific antibodies that is coated on latex beads. This crosslinking reaction results in changes in the solution turbidity and is proportional to the amount of the antigen in the samples. It is found to be linear in the HbA1c range of 2.0% - 16.0 %.

Enzymatic HbA1c assay method: Recent innovation has yielded a Direct Enzymatic HbA1c Assay TM which uses a single channel test and reports %HbA1c values directly, without the need for a separate THb test.

Assay Principle

Oxidizing agents in the lysis buffer react with the blood sample to discard low molecular weight and high molecular weight signal interfering substances. After lysis, the whole blood samples are subjected to proteolytic digestion. This process releases amino acids, including glycated valines, from the hemoglobin betachains. The Direct Enzymatic HbA1c Assay™ glycated valines serves as substrates for a specific recombinant fructosyl valine oxidase (FVO) enzyme. The recombinant FVO specifically cleaves N-terminal valines and then produces hydrogen peroxide in the presence of selective agents. This is measured using a horseradish peroxidase (POD) catalyzed reaction and a suitable chromagen.

The signal produced in the reaction is used to directly report the percentage HbA1c of the sample using a suitable linear calibration curve expressed in %HbA1c.

The Direct Enzymatic HbA1c Assay has all the advantages of both the HPLC and immunoassays methods in accuracy, specificity, applicability to chemistry analyzers and yet is cost effective, simpler and has less interferences. The direct enzymatic HbA1c test uses 2 ready-to-use liquid stable reagents . Since it does not require a separate measurement of total hemoglobin content in the samples, the

Direct Enzymatic HbA1c Assay only needs a single channel to perform the test on chemistry analyzers in comparison with some immunoassays that require a separate measurement of total hemoglobin and need two channels for thetest on chemistry analyzers.

The Direct Enzymatic HbA1c Assay™ procedure is simple and straight forward. The result of %HbA1c will be reported within 2 minutes. In addition, the reagents do not contain latex particles, and hence do not coat analyzer cuvettes and lines. Most importantly, enzymatic HbA1c assays have the highest specificity among all HbA1c assays. The direct enzymatic HbA1c method has an assay linearity range from 4 to 16%.

The enzymatic HbA1c assays are not interfered by either chemical or genetically modified hemoglobin variants. Therefore, enzymatic Hb1c tests are reliable tests, and it does not report false results regardless of the patient’s hemoglobinvariant types.

In summary, the Direct Enzymatic HbA1c Assay offers the following advantages over HPLC and Immunoassays:

a. Two reagents, liquid stable

b. No need for total hemoglobin measurement

c. Single channel on analyzers Faster, simpler and more cost effective

d. No interferences from hemoglobin variants

e. On-board blood lysis possible

f. Applicable to most analyzers.

Advantages and disadvantages of various HbA1c assay methods

Assay	Principle	Advantages	Disadvantages
Ion Exchange Chromatography	HbA1c has lower isoelectric point and migrates faster than other Hb components.	Can inspect chromograms for Hb variants. Measurements with great precision.	Variable interference from hemoglobinopathies, HbF and carbamylated Hb but the current ion exchange assays correct for HbF and carbamylated Hb does not interfere.
Boronate Affinity	Glucose binds to m-aminophenylboronic acid.	Minimal interference from haemoglobinopathies, HbF and carbamylated Hb.	Measures not only glycation of N-terminal valine on β chain, but also β chains glycated at other sites and glycated α chains.
Immunoassays	Antibody binds to glucose and between 4-10 N-terminal amino acids on β chain.	Not affected by HbE, HbD or carbamylated Hb Relatively easy to implement under many different formats.	May be affected by haemoglobinopathies with altered amino acids on binding sites. Some interference with HbF.

FACTORS AFFECTING HbA1C

1. Erythropoiesis

Increased HbA1c: iron, vitamin B12 deficiency, decreased erythropoiesis.

Decreased HbA1c: administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.

2. Altered Haemoglobin

Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.

3. Glycation

Increased HbA1c: alcoholism, chronic renal failure, decreased intra-erythrocyte pH.

Decreased HbA1c: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH.

Variable HbA1c: genetic determinants.

4. Erythrocyte destruction

Increased HbA1c: increased erythrocyte life span: Splenectomy.

Decreased A1c: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.

5. Assays

Increased HbA1c: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use.

Variable HbA1c: haemoglobinopathies.

Decreased HbA1c: hypertriglyceridaemia.

ALTERNATIVES OF HbA1C

Alternative biomarkers

1. Fructosamine

Fructosamine is a ketoamine formed from the binding of fructose to total serum protein, mostly albumin, through glycosylation.. Fructosamine assays are cheaper and easier to perform than HbA1c assays. Serum fructosamine values reflect mean blood glucose concentrations over the previous two to three weeks, which can be used clinically as markers of recent changes in glycemic control. When used in combination with other measures, it may play a role in identifying fluctuating glucose levels in DM patients with stable HbA1c. There are also several limitations

to the use of serum fructosamine measurements. The higher within-subject variation for fructosamine than that for HbA1c means that frequent measurements must be conducted. Serum fructosamine values must be adjusted if the serum albumin concentration is abnormal. Falsely low levels in relation to mean blood glucose levels will occur with rapid albumin turnover, such as in nephrotic syndrome, severe liver disease, or protein-losing enteropathy. The level of fructosamine in young children is lower than that in adults, which is also partly due to their lower serum protein concentration.

- 2.Glycated albumin

GA is the proportion of the serum GA to the total albumin. GA is similar to serum fructosamine, except that is not affected by serum albumin levels. The level of GA is approximately three times higher than that of HbA1c. Since the half-life of albumin is shorter than that of RBC, GA reflects a shorter duration, two to three weeks, of glycemic control, than that of HbA1c. GA and fructosamine are strongly associated with HbA1c and fasting glucose.

- Clinical usefulness of GA has several advantages for monitoring for glucose control. The first is that it is not influenced by abnormal RBC lifespan or variant hemoglobin. GA is a particularly useful indicator of glycemic control in hematologic disorders, such as in anemia, hemorrhage, renal anemia, pregnancy, liver cirrhosis, and neonatal DM. The second advantage is that GA may be quite useful for conditions in which glycemia improves rapidly, or in which glycemia deteriorates. rapidly, such as in fulminant type I DM. GA will provide a more accurate assessment of recent glycemia.

  Finally, when compared with HbA1c values, GA values have more correlation with postprandial glucose levels and glucose excursions. Because the glycation speed of GA is ten times faster than HbA1c, GA is likely to reflect variations in blood glucose and postprandial hyperglycemia in combination with HbA1c and its value.

- Limitations of GA has abnormal values in diseases that result in abnormal albumin metabolism. The rise of albumin metabolism leads to low GA levels in diseases including nephrotic syndrome, hyperthyroidism, glucocorticoid administration, Cushing's syndrome, and in neonates. Whereas albumin

metabolism decreases, high GA levels are seen in diseases such as liver cirrhosis and hypothyroidism.

3.1,5-anhydroglucitol

The 1-deoxy form of glucose known as 1,5-AG is a naturally occurring dietary polyol. During euglycemia, serum 1,5-AG concentrations are maintained at a constant steady state due to renal tubular reabsorption of all of the serum 1,5-AG. The normal serum concentration of 1,5-AG has been reported to be 12-40 μg/mL. Serum 1,5-AG competes with very high levels of glucose for reabsorption into the kidney.

4. Continuous glucose monitoring

Although the use of continuous glucose monitoring can accurately evaluate the glycemic variability of within-day and between-day, the current continuous glucose monitoring systems are expensive without national health insurance coverage and are not easily available in clinical practice. Furthermore, they are relatively inaccurate in the lower glucose range, and should be used in conjunction with self-monitoring of blood glucose.

MATERIALS AND METHODS

STUDY POPULATION:

The study was conducted on 100 patients who were admitted and attending OP in Govt. Rajaji hospital, Madurai.

DESIGN OF STUDY:

Prospective study.

DURATION OF STUDY:

Six months

ANTICIPATED OUTCOME:

Complete recovery from the effect of poison, with treatment or Death

INCLUSION CRITERIA:

All patients with Overt Hypothyroidism.

EXCLUSION CRITERIA:

- Diabetes mellitus (FBS>=126 mg/dl, PPBS: >=200 mg/dl)
- Impaired glucose tolerance(2h post 75g OGTT is between 140- 199 mg/dl).
- Hb< 10 g/dl
- Known hemoglobinopathies
- Renal or Liver diseases.
- Recent blood transfusions (< 3 months)
- Pregnant patients

ANTICIPATED OUTCOME

- Higher baseline HbA1c levels in overt hypothyroid patients despite having normal glucose levels.

- HbA1c fall in hypothyroid patients following treatment and achievement of euthyroid state.

DATA COLLECTION AND STUDY PROTOCOL:

A previously designed proforma was used to collect the relevant demographic and clinical details of the patients. Patients were enrolled in thestudy after informed consent.

Patients were

selected based on clinical examinations, biochemical tests. The patients were followed over a period of six months with TSH and HbA1c levels.

LABORATORY INVESTIGATIONS

- Complete blood count
- Reticulocyte count
- Fasting blood glucose
- Post prandial blood glucose(post OGTT)
- HbA1c
- TSH/T4
- Liver and renal function tests

COLLABORATING DEPARTMENTS:

Department of Biochemistry, endocrinology, pathology

ETHICAL CLEARANCE:

Obtained

CONSENT:

Individual written and informed consent

CONFLICT OF INTEREST:

Nil

FINANCIAL SUPPORT:

Self

STATISTICAL ANALYSIS:

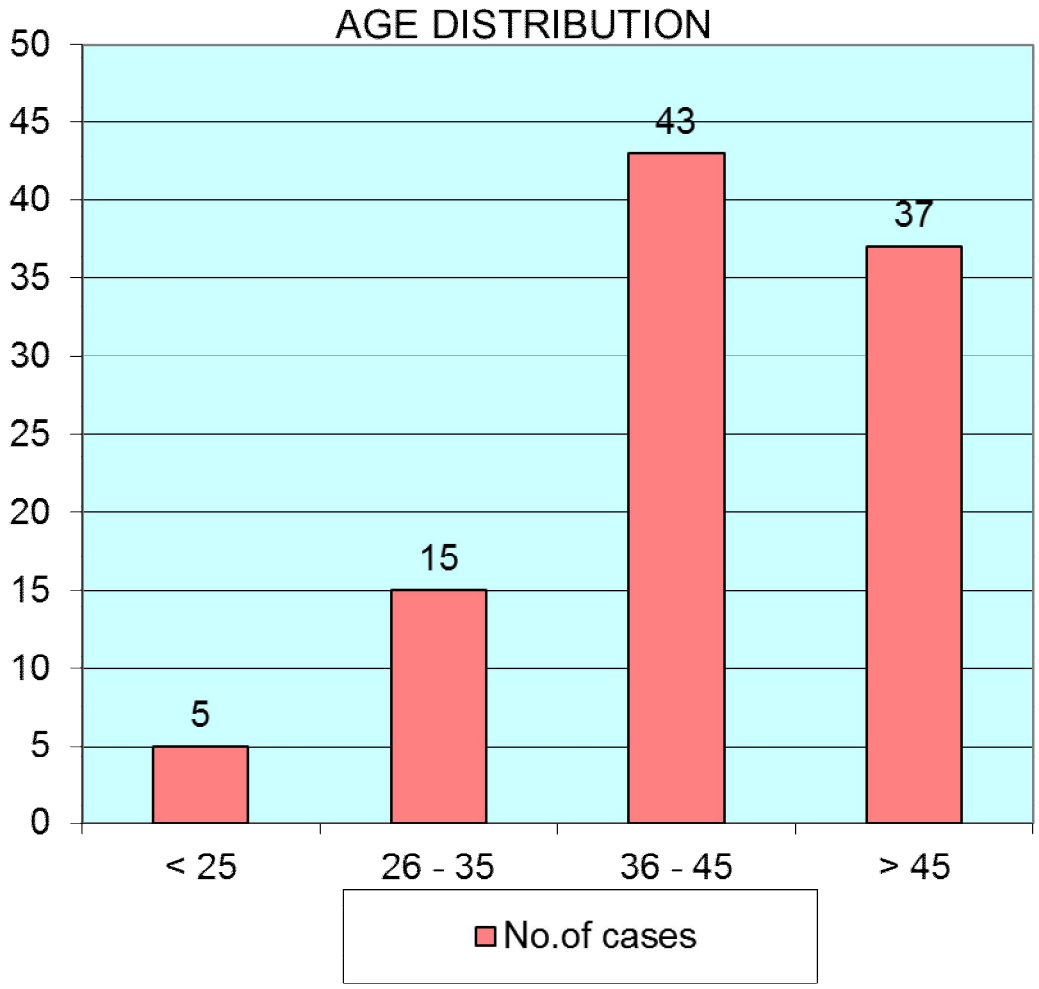
The data collected in the study was formulated into a master chart inMicrosoft office Excel and statistical analysis was done with the help ofcomputer using statistical software package SPSS V.17 for windows. Using this software, frequencies, range, mean, standard deviation and percentageswere calculated.

OBSERVATION AND RESULTS

Sample size distribution in the study group

AGE	No.of cases
≤ 25	5
26 – 35	15
36 – 45	43
> 45	37
Total	100

Out of 100 patients in the study group, majority ie. 43% belonged to the age group-(36-45). Followed by people more than 45 years ie.37%.

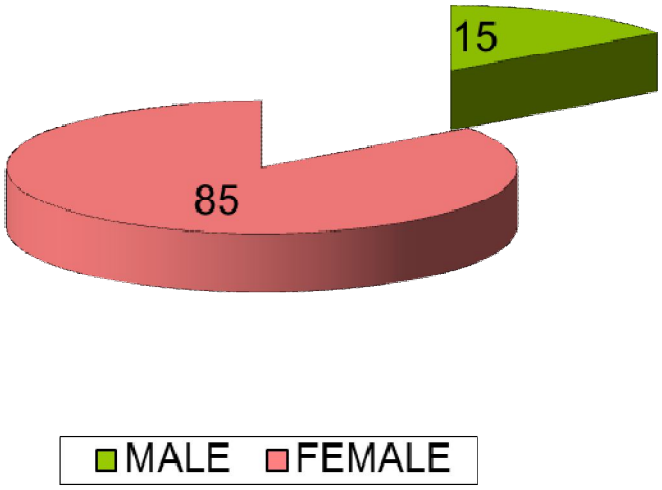

AGE DISTRIBUTION
50
45
40
35
30
25
20
15
10
5
0
43
37
15
5
< 25
26 - 35
36 - 45
> 45
No.of cases

SEX DISTRIBUTION AMONG PARTICIPANTS

SEX	No.of cases
MALE	15
FEMALE	85
Total	100

Out of the 100 study population majority were females 85% and males were only15%. This was probably bacuase hypothyroidism was more common in females in the general population.

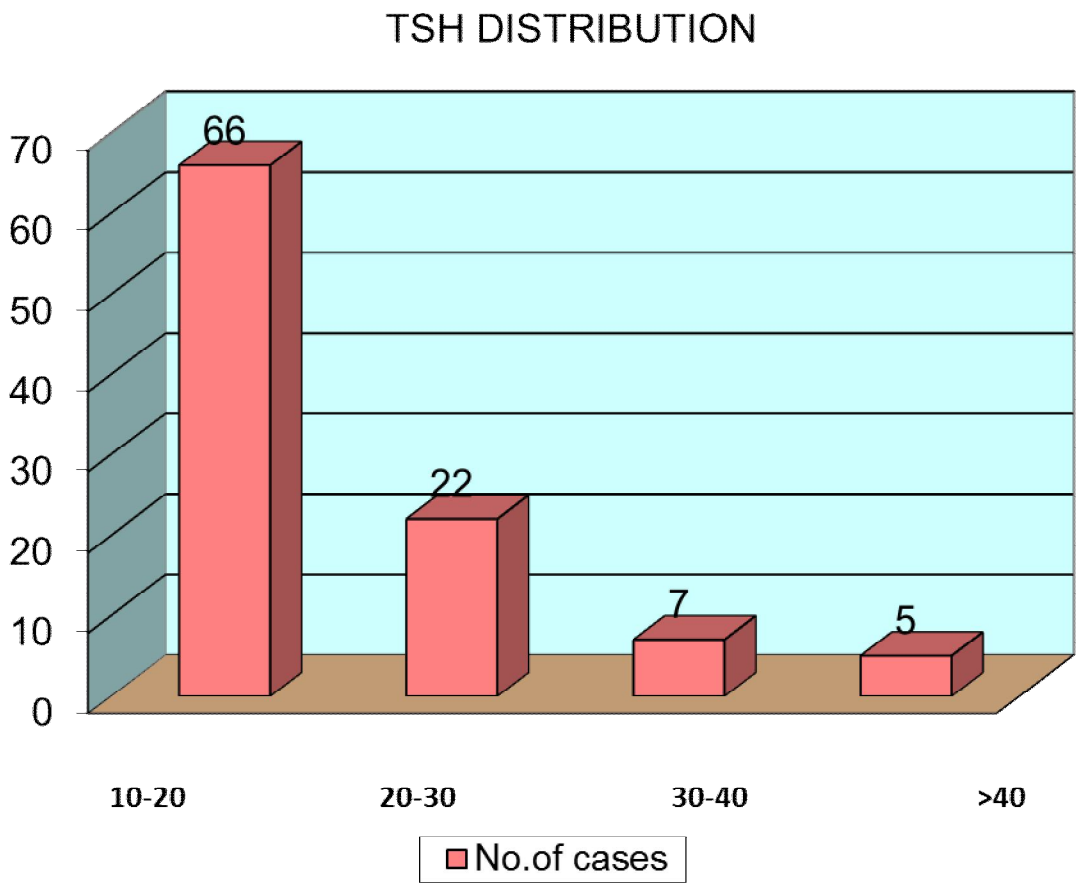
GENDER DISTRIBUTION



BASELINE TSH VALUES OF THE STUDY POPULATION.

TSH	No.of cases
10 - 20	66
21 - 30	22
31 - 40	7
> 40	5
Total	100

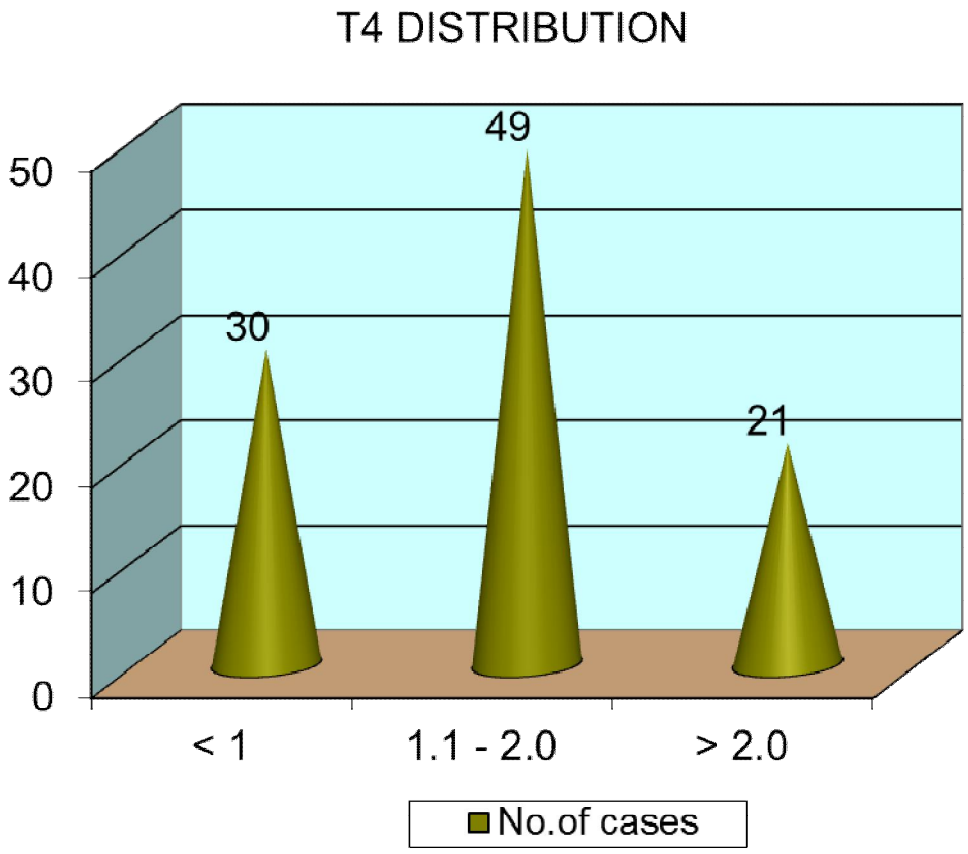
This table shows the distribution of TSH values among the study population. It is to be noted that majority of the study population ie. 66% had their TSH values between 10-20 mIU/L.


TSH DISTRIBUTION
70
60
50
40
30
20
10
0
66
22
7
5
10-20
20-30
30-40
>40
No.of cases

BASELINE TOTAL T4 IN THE STUDY POPULATION

T4	No.of cases
≤ 1	30
1.1 - 2.0	49
2 - 4.5	21
Total	100

This table shows the distribution of T4 in the study population before treatment. It can be seen that majority of the patients had a very low T4 of approximately 1.1 – 2.0. they constitute 49% of the study population.

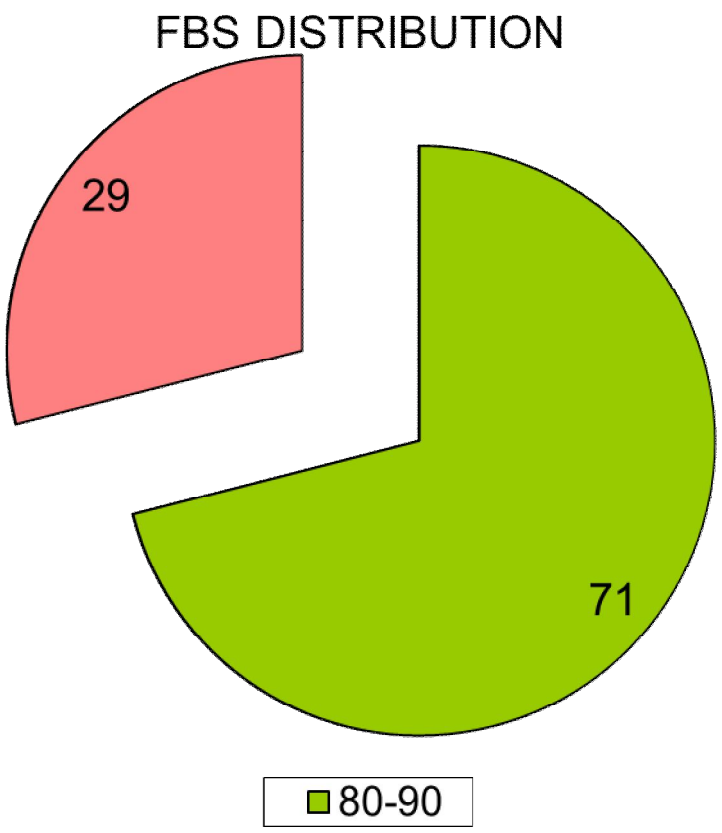

T4 DISTRIBUTION
50
40
30
20
10
0
49
30
21
< 1
1.1 - 2.0
> 2.0
No.of cases

BASELINE FASTING BLOOD SUGAR AND POST PRANDIAL BLOOD SUGARS OF THE STUDY POPULATION

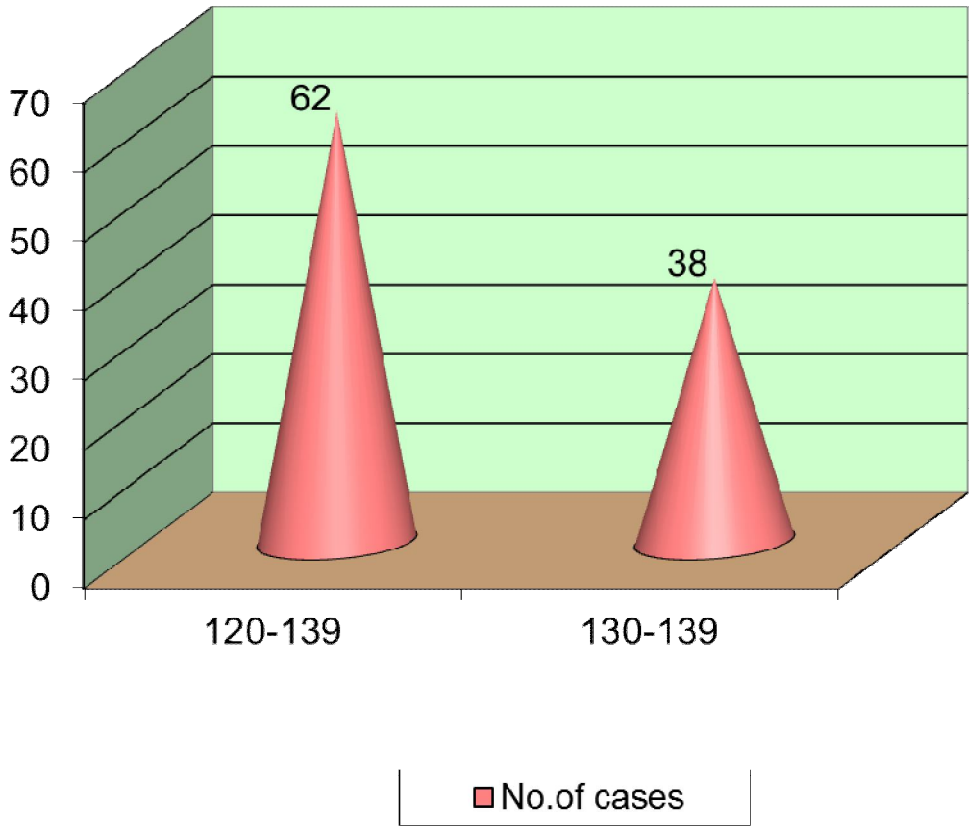
FBS	No.of cases
< 90	71
90-100	29
Total	100

PPBS	No.of cases
< 130	62
> 130	38
Total	100

From this table we infer that the patients in the study population had a baseline fasting blood sugars and post prandial blood sugars within normal limits. None had their fasting blood sugar or their post prandial blood glucose in the impaired glucose tolerance or in the diabetic range.


FBS DISTRIBUTION
29
71
80-90

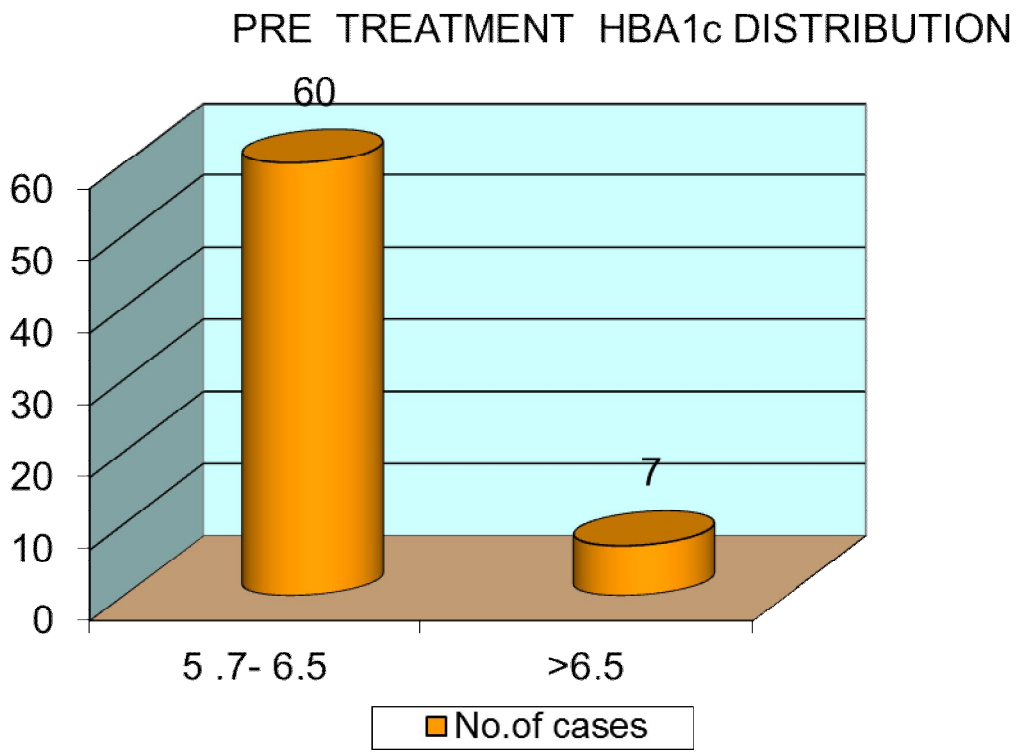
PPBS



PRE TREATMENT HbA1C

HbA1c	No.of cases
< 5 .7	33
5 .7- 6.5	60
>6.5	7
Total	100

From this chart we can infer that the baseline HbA1c was significantly high around 67% in hypothyroid patients inspite of having normal blood sugar levels.7 out of 100 patients even had HbA1c in the diabetic range.

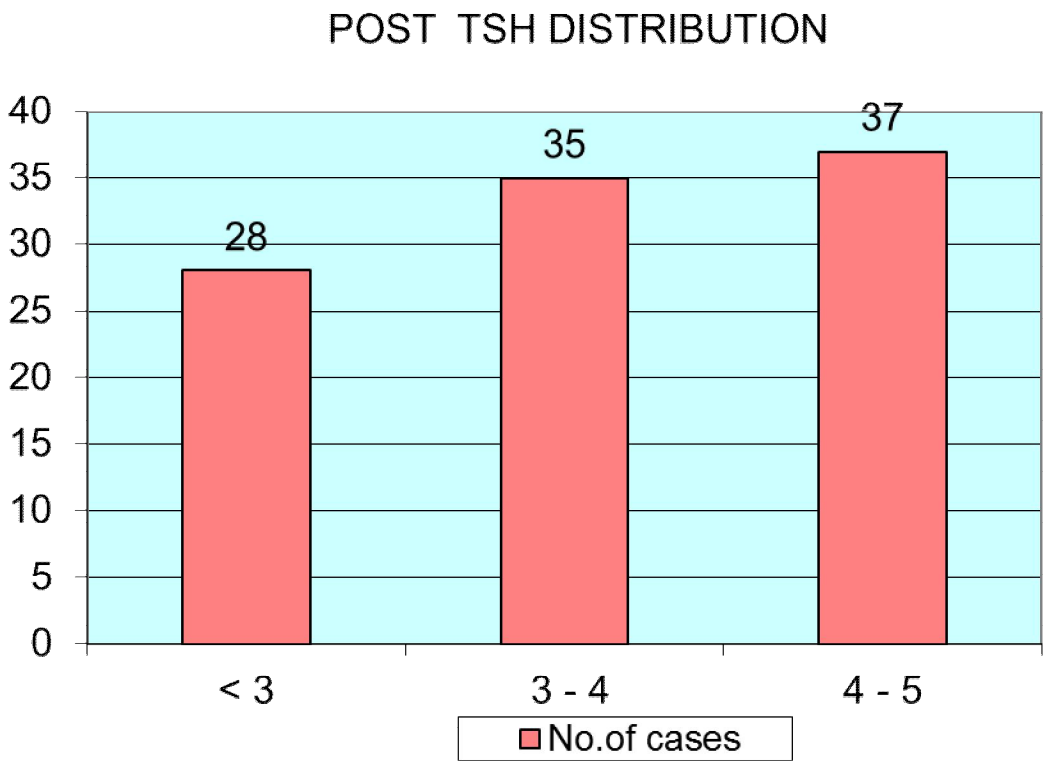

PRE TREATMENT HBA1c DISTRIBUTION
60
7
60
50
40
30
20
10
0
5 .7- 6.5
>6.5
No.of cases

After 6 months of follow up these patients were again investigated for for thyroid hormone profile (TSH, T4) FBS, PPBS and HbA1c.

The results were as follows

TSH	No.of cases
≤ 3	28
3 - 4	35
4 - 5	37
Total	100

From this chart we can see that we can see that the TSH has significant declined in our study population after thyroxine replacement.

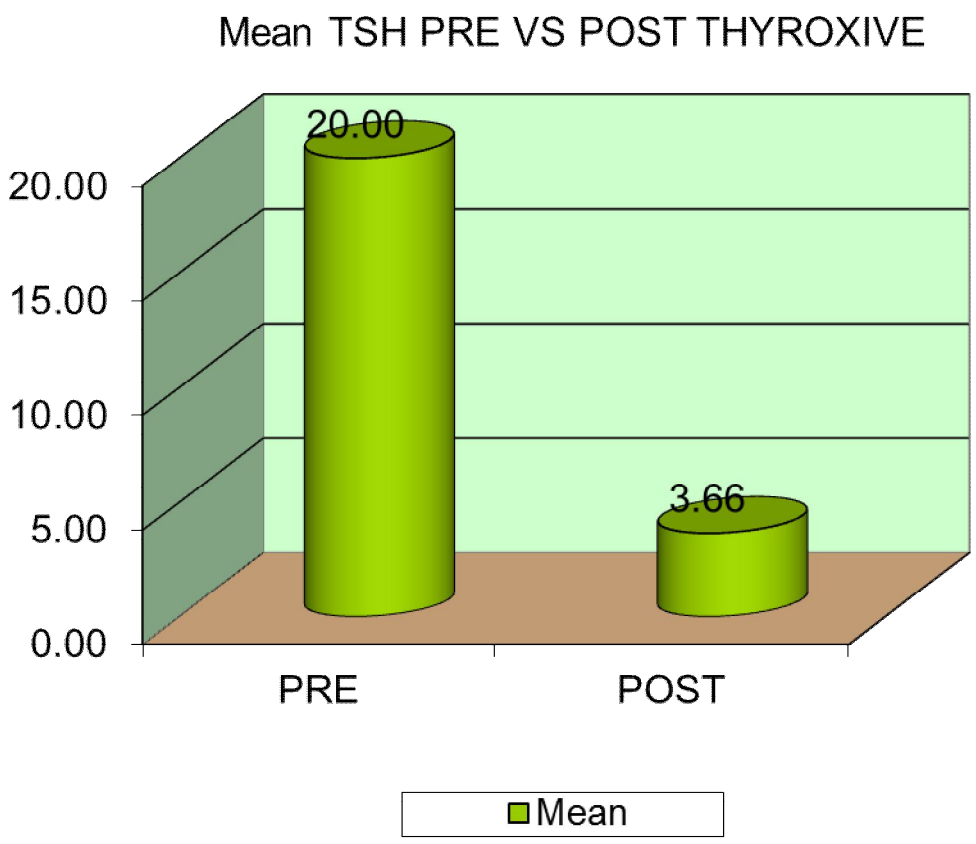

POST TSH DISTRIBUTION
40
35
30
25
20
15
10
5
0
28
35
37
< 3
3 - 4
4 - 5
No.of cases

This table compares TSH values before and after thyroxine replacement.

TSH	PRE	POST
Mean	20.00	3.66
S.D	9.16	0.81
P'	<0.001	Sig

The mean TSH before and after thyroxine treatment has significantly declined and it is statistically significant with a standarad deviation of 0.81 after treatment. P value <0.001

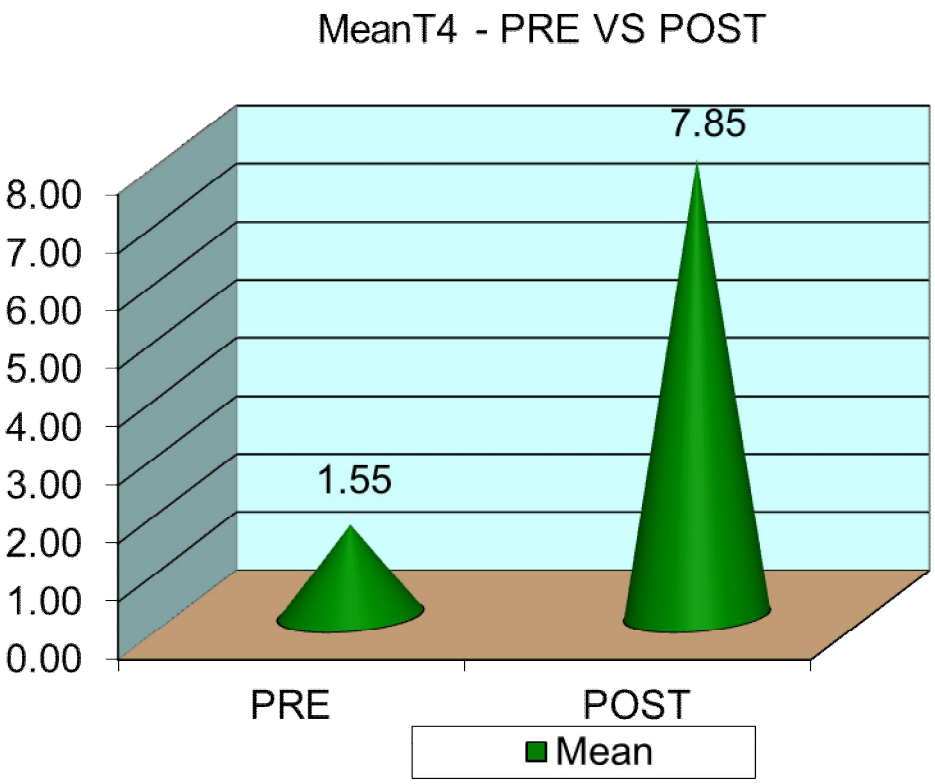
This chart compares the mean TSH levels pre and post thyroxine replacement.


Mean TSH PRE VS POST THYROXIVE
20.00
3.66
20.00
15.00
10.00
5.00
0.00
PRE
POST
Mean

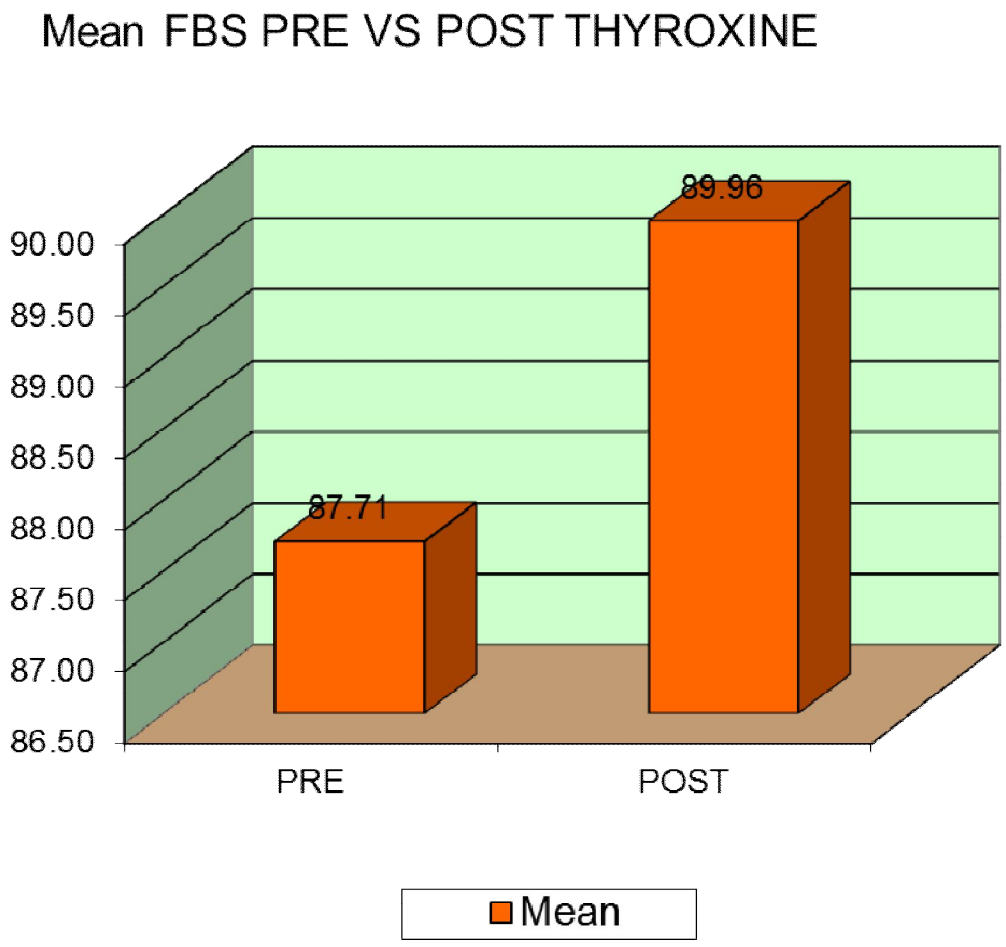
The table shows the difference in T4 levels before and after thyroxine replacement.

T4	PRE	POST
Mean	1.55	7.85
S.D	0.81	1.94
P'	<0.001	Sig

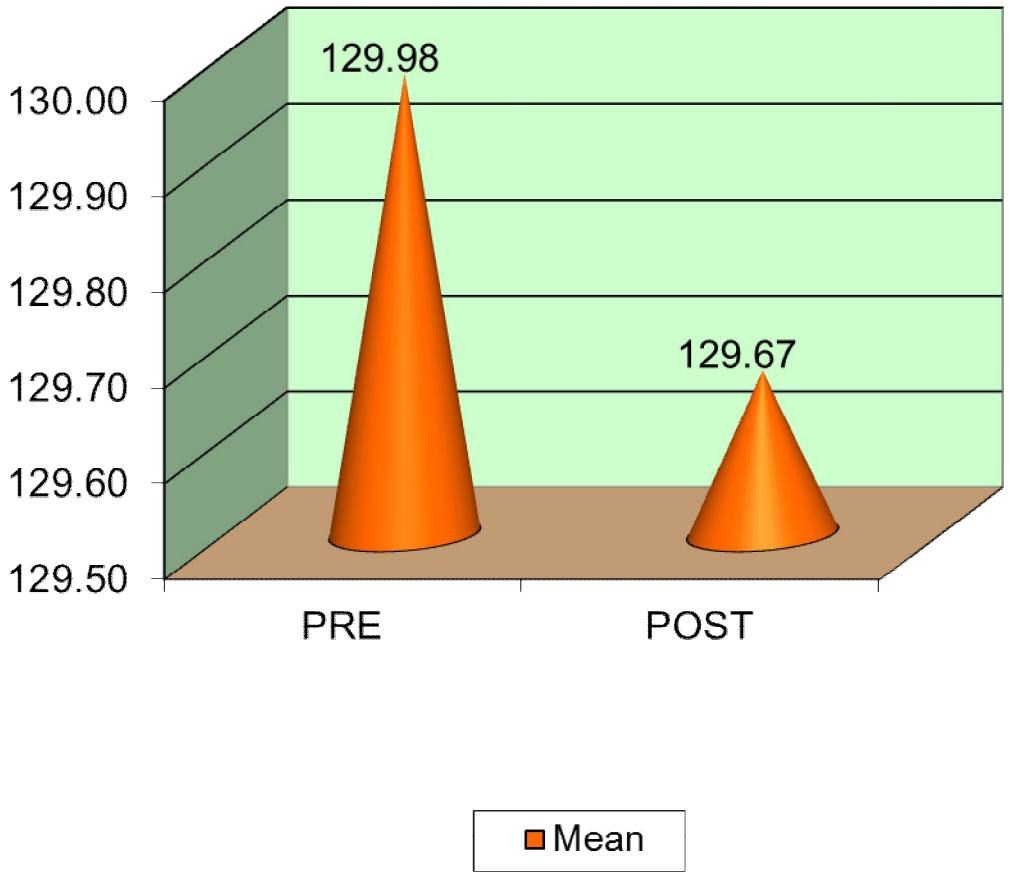
From this table we see that the T4 levels have significantly increased post treatment with a standard deviation of 1.94. p value <0.001 which is statiscally significant.


MeanT4 - PRE VS POST
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
1.55
7.85
PRE
POST
Mean

Although the thyroid hormone profile showed a significant change after thyroxine replacement the FBS and PPBS remained unchanged before and after treatment



Mean PPBS - PRE VS POST THYROXINE



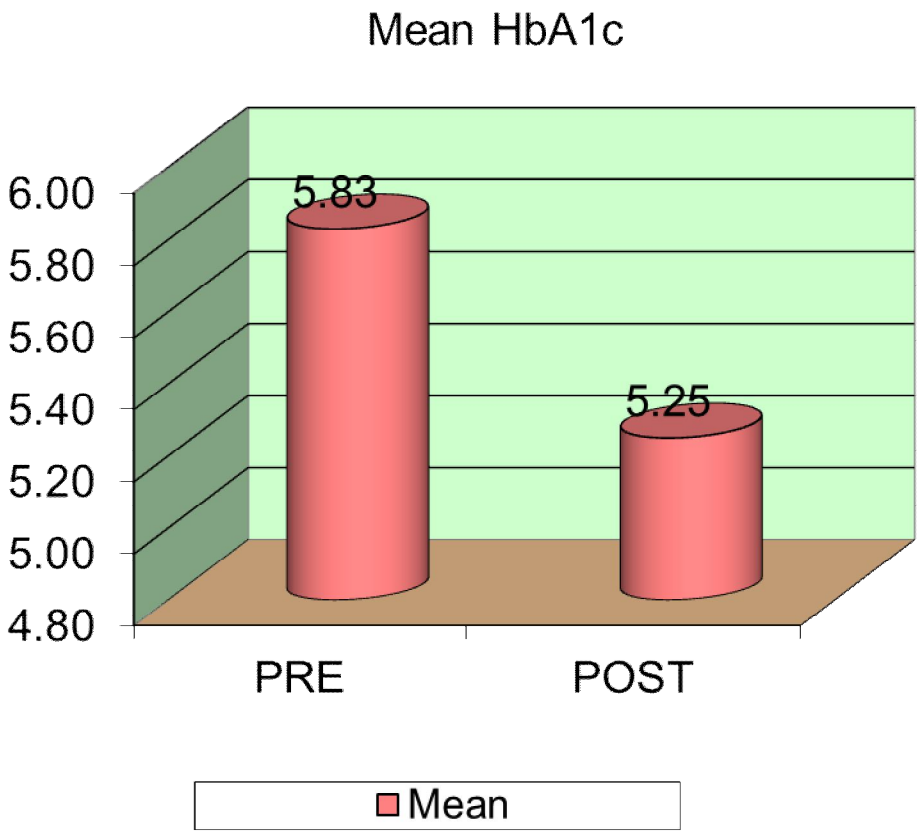
HBA1C POST THYROXINE REPLACEMENT

HbA1c	No.of cases
< 5.7	100
< 5.7- 6.5	0
> 6.5	0
Total	100

This table shows that all the patients in the study population had a normal HbA1c level after thyroxine replacement and achievement of a euthyroid state.

HbA1c	PRE	POST
Mean	5.83	5.25
S.D	0.35	0.21
P'	<0.001	Sig

The mean HbA1c significantly decreased post thyroxine replacement and achievement of euthyroidal state. P value is <0.001 which is statistically significant.



DISCUSSION

In our study majority of the patients belong to age group 36-45(43%). Females were more in number (85%).

The baseline TSH values on an average was between (10-20) in 66% of the study population. T4 levels were between 1.1-2.0 in 49% of patients.In these patients the post treatment FBS and PPBS were with normal limits.The HbA1c estimation was done and was found to be increased. The average HbA1c was around 5.83%.

This lead to false diagnosis of dysglycemia in 67% of patients. False diagnosis of impaired glucose tolerance -60% and diabetes was 7%.This false elevation of HbA1c was also demonstrated by Kim and cols who showed that HbA1c in 45 hypothyroid patients was higher than in control group A study by Anantarapu et al. also demonstrated false elevation of HbA1c values in patients withhypothyroidism which was lowered by thyroid hormone replacementwithout any change in fasting or OGTT values.

After thyroxine replacement and achievement of euthyroidal state ,follow up was done for 3 months post achieving euthyroidal state on account of approximately 120 days of life span of RBC.

The T4 and T4 on the average was found to be TSH-3.66 and T4- 7.85 within normal range, although there was no difference in fasting and post prandial blood sugars the mean HbA1c decreased to 5.25%

These findings were similar to a study done by Kwon HS et al published in diabetes care journal in 2010 which showed no changes in FBS and PPBS following correction of hypothyroidism.

CONCLUSION

Its concluded from the above study that HbA1c are falsely elevated out of proportion to the level of glycemia in patients with hypothyroidism which leads to false diagnosis of dysglycemia and it is lowered without any change in blood sugar levels after thyroine replacement and achievement of a euthyroidal state.

Therefore in hypothyroid patients diagnosis of pre diabetes or diabetes should only be based on fasting blood glucose and post prandial blood glucose .

So we conclude that HbA1c is not a valid test for diagnosis of prediabetes or diabetes in the presence of hypothyroidism.

Limitations

- The study had a relatively short period of follow up.

- Absence of a control group.

PROFORMA

Name:

Age / Sex:

Occupation:

Presenting complaints:

Past History:

H/o diabetes mellitus, systemic hypertension, renal/ liver diseases, thyroid disorders, previous blood transfusions.

Clinical Examination:

General Examination:

Consciousness

Pallor

Jaundice

Clubbing

Lymphadenopathy

Hydration status

Vitals:

PR

BP

RR

SpO2

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations:

- Complete blood count
- Reticulocyte count
- Liver function test,
- Renal function test,
- Fasting and post prandial blood glucose
- TSH,
- HbA1c

Abbreviations

FBS- Fasting blood sugar

PPBS- Post prandial blood sugar

TSH- Thyroid stimulating hormone

T4- Thyroxine

ANNEXURE

MASTER CHART

			PRE					POST				
S. No.	Age	Sex	TSH	T4	FBS	PPBS	HbA1c	TSH	T4	FBS	PPBS	HbA1c
1	25	M	15	2.1	86	126	5.4	2.2	7.2	86	122	5.1
2	44	F	23	1.2	85	129	5.3	3.4	8.4	89	124	5
3	47	M	11	1.9	99	132	5.4	5	5.1	95	137	5.1
4	19	F	12	0.9	95	135	5.1	2.9	6.1	96	139	5
5	30	F	51	1.1	84	138	6.1	3.2	6.3	81	134	5.3
6	55	M	14	1.6	83	128	6.3	4.8	5.9	87	130	5.1
7	49	F	22	1.8	86	127	5.9	2.3	6.3	93	126	5.2
8	42	M	20	2.6	92	126	6.3	3.4	8.2	95	124	5.6
9	40	F	12	4.1	91	125	5.2	2.9	5.5	97	126	5
10	41	F	21	2.2	87	139	5.5	3.4	10.6	82	129	5.1
11	38	M	13	0.8	91	137	5.6	2.8	9.2	80	130	5.2
12	39	F	20	0.7	80	135	5.4	2.9	9.3	95	132	5.1
13	37	M	14	2.4	83	133	5.8	4.1	9.8	96	134	5.3
14	28	M	20	1.1	88	130	6.1	4.4	8.4	83	125	5.6
15	30	F	24	1.4	90	122	6	4.6	6.9	84	126	5.1
16	51	F	35	1.5	93	120	6.6	4.2	4.6	86	130	5.6
17	27	M	42	2.6	88	124	6.3	3.8	4.8	85	134	5.6
18	21	M	14	2	97	126	5.9	3.9	5.9	98	120	5.2
19	36	F	19	1.7	98	129	5.6	3.7	7.8	97	128	5.1
20	35	F	41	0.8	82	127	5.8	4.2	7.7	96	127	5
21	48	M	34	0.6	84	130	6.7	4.4	9.2	84	136	5.4
22	43	M	40	1.1	86	131	6.2	5	10.5	87	137	5.3

23	49	F	18	1.9	87	130	5.8	2.1	11	89	139	5.4
24	39	M	21	0.9	86	138	6.1	4.7	10.7	92	120	5.2
25	42	F	28	0.5	80	137	6.5	2.9	6.9	94	121	5.3
26	47	M	20	0.8	81	129	6.3	3.8	7.7	96	127	5.1
27	52	F	18	2.2	84	130	5.9	3.7	8.4	88	130	5.2
28	54	F	30	1.2	86	122	5.4	3.4	5.5	87	125	5
29	50	M	15	1.9	88	124	5.5	4.4	6.1	86	134	5.1
30	37	M	12	0.9	83	137	5.6	3.4	6.3	82	127	5.2
31	39	F	45	1.1	93	129	5.8	5	5.9	83	136	5.3
32	36	F	10	1.6	94	132	5.9	2.9	6.3	86	131	5.1
33	50	F	14	1.8	96	135	5.7	3.2	8.2	84	124	5.3
34	36	F	13	2.6	90	138	5.9	4.8	5.5	96	137	5.4
35	34	M	11	4.1	91	128	6.1	2.3	10.6	94	139	5.1
36	37	F	23	2.2	86	127	6.3	3.4	9.2	91	134	5.5
37	38	M	11	0.8	81	126	5.8	2.9	9.3	96	130	5.2
38	42	F	12	0.7	85	125	5.3	3.4	9.8	94	126	5
39	45	F	25	2.4	99	139	5.4	2.8	8.4	96	124	5.1
40	36	M	14	1.1	95	137	5.1	2.9	6.9	91	126	5
41	47	F	22	1.4	84	135	6.1	4.1	4.6	93	129	5.3
42	38	M	20	1.5	83	133	6.3	4.4	4.8	86	130	5.4
43	48	F	12	2.6	86	130	5.9	4.6	5.9	89	132	5.1
44	45	F	21	2	92	122	6.3	4.2	7.8	95	134	5.4
45	52	M	13	1.7	91	120	5.2	3.8	7.7	96	125	5
46	47	F	20	0.8	87	124	5.5	3.9	9.2	81	126	5.1
47	25	M	14	0.6	91	126	5.6	3.7	10.5	87	130	5.3
48	34	F	20	1.1	80	129	5.4	4.2	11	93	134	5
49	39	F	24	1.9	83	127	5.8	4.4	10.7	95	120	5.2
50	37	F	35	0.9	88	130	6.6	5	6.9	97	128	5.4
51	42	F	52	0.5	90	131	6.5	2.1	8.2	82	127	5.3
52	50	M	14	0.8	93	130	6.1	4.7	5.5	80	136	5.2
53	47	F	19	1.2	88	138	6.3	2.9	10.6	95	137	5.6
54	46	M	20	1.9	97	137	5.9	3.8	9.2	96	139	5.2
55	49	F	34	0.9	98	129	5.6	3.7	9.3	83	120	5.1
56	36	F	40	1.1	82	130	5.8	3.4	9.8	84	121	5.1
57	55	M	18	1.6	84	122	6.1	2.1	8.4	86	127	5.6
58	49	M	21	1.8	86	124	6.2	4.7	6.9	85	130	5.3
59	42	M	28	2.6	87	129	5.8	2.9	4.6	98	125	5.2
60	40	F	20	4.1	86	132	6.1	3.8	4.8	97	134	5.4
61	41	F	18	2.2	80	135	6.2	3.7	5.9	96	127	5.2
62	38	F	30	0.8	81	138	6.5	3.4	7.8	84	136	5.6
63	39	M	15	0.7	84	128	5.9	4.4	7.7	87	124	5.2
64	37	M	12	2.4	86	127	5.4	3.4	9.2	89	137	5
65	52	F	11	1.1	88	126	5.5	5	10.5	92	139	5.1

66	30	F	10	1.4	83	125	5.6	2.9	11	90	134	5.2
67	54	M	14	1.5	93	139	5.8	3.2	10.7	96	130	5.3
68	27	M	13	2.6	94	137	5.9	4.8	6.9	88	126	5.3
69	29	F	11	2	96	135	5.7	2.3	10.5	87	124	5.1
70	36	F	23	1.7	90	133	5.9	3.4	11	86	126	5.2
71	35	F	11	0.8	91	130	6.1	2.9	10.7	82	129	5.6
72	37	F	12	0.6	86	122	6.3	3.4	6.9	83	130	5.6
73	33	F	25	1.1	88	120	5.3	2.8	7.7	86	132	5
74	29	F	14	1.9	97	124	5.4	2.9	8.4	84	134	5.1
75	39	M	22	0.9	98	126	5.1	4.1	5.5	96	125	5
76	42	M	20	0.5	82	129	6.1	2.3	6.1	94	126	5.4
77	47	F	12	0.8	84	127	6.3	3.4	6.3	91	130	5.6
78	52	M	21	1.2	86	130	5.9	2.9	5.9	96	134	5.1
79	54	M	13	1.9	87	131	6.3	3.4	6.3	94	120	5.6
80	50	F	20	0.9	86	130	5.2	2.8	8.2	96	128	5
81	30	M	14	1.1	80	138	5.5	2.9	5.5	91	127	5.1
82	38	F	20	1.6	81	137	5.6	4.1	10.6	96	136	5.2
83	50	M	24	1.8	84	129	5.4	4.4	9.2	88	137	5
84	51	F	14	2.6	86	130	5.8	4.6	9.3	87	139	5.1
85	24	F	11	4.1	88	122	6.1	4.2	9.8	86	139	5.6
86	34	M	14	2.2	83	124	6	3.8	8.4	82	120	5.1
87	37	M	19	0.8	93	129	6.1	3.9	6.9	83	121	5.3
88	38	F	13	0.7	88	132	6.3	3.7	10.5	86	127	5.6
89	51	F	34	1.1	97	135	5.9	4.2	11	84	130	5.2
90	45	F	17	1.1	98	138	5.6	4.4	10.7	96	125	5.1
91	51	M	18	1.4	82	128	5.8	5	6.9	94	134	5
92	47	F	21	1.5	84	127	6.6	2.1	7.7	91	127	5.5
93	50	M	28	2.6	86	126	6.2	4.2	8.4	96	136	5.3
94	47	F	20	2	87	125	5.8	3.8	5.5	94	124	5.2
95	45	F	18	1.7	86	139	6.1	3.9	6.1	96	137	5.6
96	51	F	16	0.8	80	137	6.2	3.7	6.3	91	139	5.4
97	42	F	15	0.6	81	135	6.3	4.2	5.9	93	134	5.6
98	46	F	12	1.1	84	133	5.9	4.4	6.3	86	130	5.1
99	52	F	11	1.9	86	130	5.4	5	8.2	89	126	5.1
100	41	F	10	0.9	88	122	5.5	2.1	5.5	95	124	5.2

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Research Topic	:	Effects of thyroxine replacement on HbA1c levels in non diabetic patients with overt hypothyroidism
Ethical Committee as on	:	31.03.2018

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